Tetrahedron Letters 52 (2011) 1901–1904

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Novel synthetic method for allylic amination of cyclic allylic ethers using chlorosulfonyl isocyanate

Sang Hwi Lee [a], In Su Kim [b], Qing Ri Li [a], Guang Ri Dong [a], Young Hoon Jung [a,*]

[a] School of Pharmacy, Sungkyunkwan University, Suwon 440-746, Republic of Korea
[b] Department of Chemistry, University of Ulsan, Ulsan 680-749, Republic of Korea

ARTICLE INFO

Article history:
Received 13 December 2010
Revised 1 February 2011
Accepted 9 February 2011
Available online 13 February 2011

Keywords:
Chlorosulfonyl isocyanate
Amination
Allylic ether
Allylic carbamate
1-Aminoindane
1-Aminotetraline

ABSTRACT

The introduction of amines to allylic or benzylic position of cyclic compounds with chlorosulfonyl isocyanate is developed in high to excellent yields. This method provides a novel access to biologically active compounds including the framework of 1-aminoindanes, 1-aminotetralines, and 1-amino-2-hydroxy cyclic compounds. Mechanistic evidence for the reaction pathway is also provided.

Considerable effort has been devoted in the last decades toward new methods for forming carbon–nitrogen bonds. Traditional methods can be divided into two large categories such as nucleophilic substitution[1] and direct amination.[2] Representative examples for nucleophilic substitution include metal-catalyzed nucleophilic substitutions,[1a–c] Mitsunobu reactions,[1d] Overmann rearrangement,[1e] and Gabriel amination.[1f,1g] The direct amination methods involve the nitrene addition,[2a] [2,2]- or [2,3]-cycloaddition reactions,[2b,c] and reductive amination.[2d] In particular, cycloaddition reactions between alkenes and an imine moiety in chlorosulfonyl isocyanate have found great utility in synthetic chemistry and are now valuable tools that are employed routinely.[3] As a result, carbon–nitrogen bond formation using chlorosulfonyl isocyante can often be found as common synthetic steps in numerous total syntheses of biologically active natural and unnatural compounds, and their synthetic derivatives.[4] In contrast, an alternative chemical reaction was found to afford allylic carbamates from allylic ethers using chlorosulfonyl isocyante.[5] Moreover, this methodology was applied to the total synthesis of biologically active polyhydroxylated alkaloids.[6] This transformation is an elegant example of avoiding prefunctionalization for the introduction of an amine moiety, and for avoiding post-manipulation such as protection of the amine functionality.

As a part of an ongoing research program aimed at the effective total synthesis of biologically active cyclic natural products and drugs, we envisioned the regioselective allylic amination of cyclic allylic ethers to give cyclic allylic amine compounds, which can be effectively transformed into biologically active natural and unnatural compounds, that is, rasagiline,[7] sertraline,[8] abacavir,[9] and acarbose,[10] as shown in Figure 1.

The initial study focused on the reaction of benzyl cyclohex-2-enyl ether (**1a**) with CSI by varying the solvent and temperature to optimize the yield, and the results are summarized in Table 1.[11] The reaction in methylene chloride at −78 °C and 0 °C furnished the corresponding carbamate **2a** in 78% and 85% yield, respectively (Table 1, entries 1 and 2).[12] However, the reaction in a nonpolar solvent, such as toluene and hexanes, provided slightly lower reaction rates and chemical yields (Table 1, entries 3–5).

The optimal reaction conditions established for the allylic amination of cyclic benzylic ether **1a** were applied to cyclic allylic ethers **1b**–**e** and cyclic aliphatic ether **1f**, as shown in Table 2.

Treatment of cyclopentenyl ether **1b** with CSI in methylene chloride at 0 °C afforded the corresponding carbamate **2b** in 81% yield (Table 2, entry 2). In the case of cyclohexenyl ethers **1c** and **1d**, the desired products **2c** and **2d** were generated in good yield, regardless of the hydroxyl protection groups (Table 2, entries 1, 3, and 4). The introduction of a methyl moiety at the 3-position decreased the reaction rate slightly (Table 2, entry 5). However, the reaction of cyclohexyl benzyl ether **1f** was ineffective, even at an increased reaction temperature and time under otherwise identical conditions (Table 2, entry 6). This is presumably due to the formation of a relatively unstable secondary carbocation intermediate, compared to the allylic secondary one.

* Corresponding author. Tel.: +82 31 290 7711; fax: +82 31 290 7773.
E-mail address: yhjung@skku.ac.kr (Y.H. Jung).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.02.036

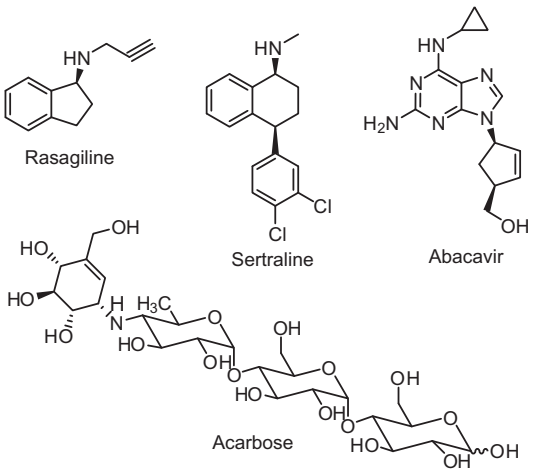
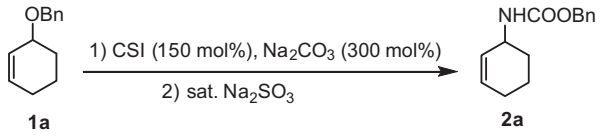


Figure 1. Biologically active compounds containing 1-amino cycloallylic or benzocylic scaffold.

Table 1
Optimization of the reaction of benzyl cyclohex-2-enyl ether (**1a**) with CSI



Entry	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	CH_2Cl_2	−78	1	78
2	CH_2Cl_2	0	1	85
3	Toluene	−78	8	70
4	Toluene	0	4	75
5	*n*-Hexanes	0	8	75

[a] Isolated yield of pure materials.

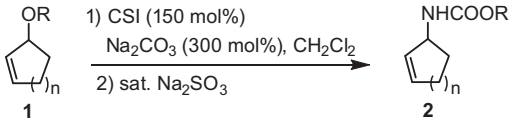
Next, the reaction of bicylic benzylic ethers **3a** with CSI was examined. After further optimization, 1-benzyloxy-1,2,3,4-tetrahydro-naphthalene (**3a**) was converted to the corresponding product **4a** at −78 °C for 3 h under otherwise identical conditions. However, the reaction between compound **3a** and CSI above 0 °C afforded compound **4a** in low yield (50%) and 1,2-dihydronaphthalene as the eliminated byproduct in 43% yield. With the optimal reaction condition established, the substrate scope was explored, as shown in Table 3.

Treatment of 1-benzyloxy indane **3b** and 1-methoxy indane **3c** with CSI under these standard conditions gave the desired products **4b** and **4c**, respectively, in excellent yield (Table 3, entries 2 and 3). However, when the benzyloxy group was located at the C-2 position, the amination product **4d** was not formed, even at an increased reaction temperature and time under otherwise identical conditions. This is presumably due to the formation of a relatively unstable secondary carbocation intermediate, compared to the benzylic secondary one. (Table 3, entry 4). In addition, 4-(benzyloxy)chroman **3e** and 9-(benzyloxy)-9*H*-fluorene **3f** were converted into compound **4e** (59%) and compound **4f** (70%), respectively, even though this required an increased reaction temperature and an extended reaction time, as shown in entries 5 and 6. In addition, 1,2-*anti*-dibenzyloxy tetraline **3g** led to the formation of the C-1 adduct **4g** with excellent regioselectivity and *anti*-diastereoselectivity of 99 > 1 (Table 3, entry 7).

To gain further insight into the reaction mechanism, additional experiments were performed using isotopically labeled allylic ether (*deuterio*-**1a**) under different solvents. As shown in Table 4, the incorporation of deuterium is dependent on the dielectric constant of the solvent. In particular, the use of *n*-hexanes provided a mixture of *deuterio*-product **5a** and *iso*-*deuterio*-product **5b** at the interior allylic position (95%) and the exterior vinylic position (5%).

A plausible reaction mechanism appears based on isotopically labeled experiments, as outlined in Figure 2. The initial attack by the oxygen of benzyl ether to CSI delivers an oxonium ion (**I**),

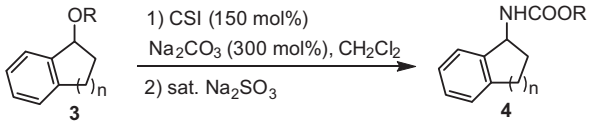
Table 2
Reaction of cyclic allylic ethers **1a**–**e** and cyclic aliphatic ether **1f** with CSI

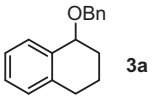
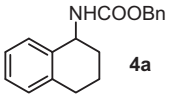
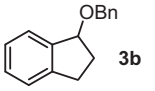
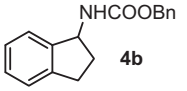
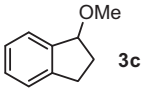
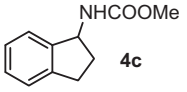
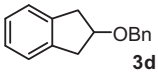
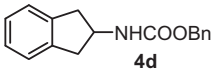
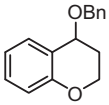
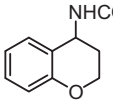
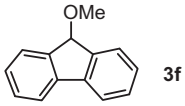
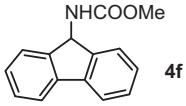
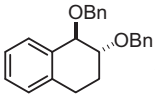
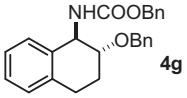


Entry	Allylic ether	Product	Temp (°C)	Time (h)	Yield[a] (%)
1	 **1a**	 **2a**	0	1	85
2	 **1b**	 **2b**	0	1	81
3	 **1c**	 **2c**	0	1	83
4	 **1d**	 **2d**	0	1	70
5	 **1e**	 **2e**	0	2	70
6	 **1f**	 **2f**	rt	24	No reaction

[a] Isolated yield of pure materials.

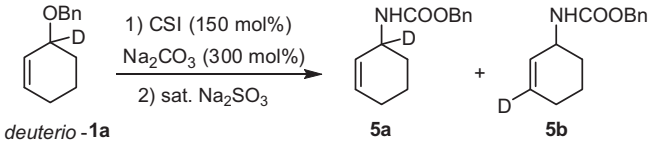
Table 3
Reaction of bicylic benzylic ethers **3a**–**g** with CSI



Entry	Allylic ether	Product	Temp (°C)	Time (h)	Yield[a] (%)
1	 **3a**	 **4a**	−78	3	82
2	 **3b**	 **4b**	−78	1	90
3	 **3c**	 **4c**	−78	1	86
4	 **3d**	 **4d**	rt	24	No reaction
5	 **3e**	 **4e**	rt	12	59
6	 **3f**	 **4f**	rt	12	70
7	 **3g**	 **4g**	−40	24	68

[a] Isolated yield of pure materials.

Table 4
Isotopically labeled experiments



Entry	Solvent	Dielectric constant (°C)	Time (h)	Yield[a] (%)	Ratio[b] (**5a**:**5b**)
1	CH_3NO_2	35.87 (30)	1	80	81:19
2	CH_2Cl_2	9.14 (20)	1	79	91:9
3	*n*-Hexanes	1.90 (20)	10	80	95:5

[a] Isolated yield of pure materials.
[b] Ratio was determined by ^{1}H NMR and ^{2}H NMR analysis.

which can be converted to the *deuterio*-product **5a** as a major compound through a 4-centered transition structure (**IIa**) according to a S_Ni mechanism. This is consistent with the results of isotopic labeling under nonpolar *n*-hexanes solvent, compared to relatively polar nitromethane and dichloromethane solvents. Another plausible S_N1 mechanism can be in competition with the S_Ni mechanism. However, this reaction may be partially proceed via S_N1 mechanism due to the incomplete orbital overlap between p orbital of the double bond and p orbital of cyclic allylic sp^2 carbocation in the reaction intermediate (**IIb**).

In conclusion, we have reported the introduction of protected amines to the ring system by a treatment of various alkyl ethers at the allylic and benzylic positions with chlorosulfonyl isocyanate in high yield. These aminations are believed to proceed through a S_Ni mechanism. This synthetic methodology can be applied easily to the preparation of various biologically active natural products and drugs containing a cyclic amine moiety.

Acknowledgments

This research was supported by a National Research Foundation Grant (NRF-2009-0074658) and the Ministry of Knowledge Economy for the Regional Innovation System program in 2010 (No. B0012306).

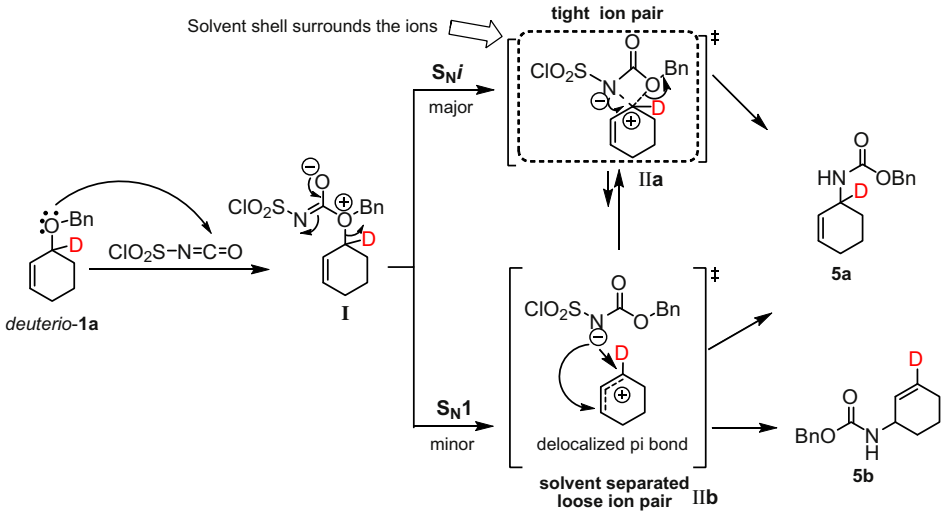


Figure 2. Proposed reaction pathway (S_Ni vs S_N1).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.036.

References and notes

1. (a) Műller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795; (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; (c) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675; (d) Mitsunobu, O. *Synthesis* **1981**, 1; (e) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597; (f) Gibson, M. S.; Bradshaw, R. W. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 919; (g) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285.
2. (a) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223; (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.
3. (a) Ulrich, H. *Chem. Rev.* **1965**, *65*, 369; (b) Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172; (c) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389; (d) Szabo, W. A. *Aldrichim. Acta.* **1977**, *10*, 23; (e) Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437.
4. (a) Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675; (b) Roberson, C. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 11342; (c) Picard, J. A.; O'Brien, P. M.; Sliskovic, D. R.; Anderson, M. K.; Bousley, R. F.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1996**, *39*, 1243.
5. (a) Dong, G. R.; Li, Q. R.; Woo, S. H.; Kim, I. S.; Jung, Y. H. *Arch. Pharm. Res.* **2008**, *31*, 1393; (b) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2005**, *46*, 1079; (c) Jung, Y. H.; Kim, J. D. *Arch. Pharm. Res.* **2005**, *28*, 382; (d) Kim, J. D.; Zee, O. P.; Jung, Y. H. *J. Org. Chem.* **2003**, *68*, 3721; (e) Kim, J. D.; Han, G.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2003**, *44*, 733; (f) Jung, Y. H.; Kim, J. D. *Arch. Pharm. Res.* **2003**, *26*, 667; (g) Kim, J. D.; Han, G.; Jeong, L. S.; Park, H.-J.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2002**, *58*, 4395; (h) Jung, Y. H.; Kim, J. D. *Arch. Pharm. Res.* **2001**, *24*, 371; (i) Kim, J. D.; Lee, M. H.; Lee, M. J.; Jung, Y. H. *Tetrahedron Lett.* **2000**, *41*, 5073; (j) Jung, Y. H.; Kim, J. D. *Arch. Pharm. Res.* **2000**, *23*, 574.
6. (a) Kim, I. S.; Li, Q. R.; Dong, G. R.; Kim, Y. C.; Hong, Y. J.; Lee, M.; Chi, K.-W.; Oh, J. S.; Jung, Y. H. *Eur. J. Org. Chem.* **2010**, 1569; (b) Kim, I. S.; Li, Q. R.; Dong, G. R.; Woo, S. H.; Park, H.-j.; Zee, O. P.; Jung, Y. H. *Synlett* **2008**, 2985; (c) Kim, I. S.; Ryu, C. B.; Li, Q. R.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2007**, *48*, 6258; (d) Kim, I. S.; Li, Q. R.; Lee, J. K.; Lee, S. H.; Lim, J. K.; Zee, O. P.; Jung, Y. H. *Synlett* **2007**, 1711; (e) Kim, I. S.; Lee, H. Y.; Jung, Y. H. *Heterocycles* **2007**, *71*, 1787; (f) Kim, I. S.; Kim, S. J.; Lee, J. K.; Li, Q. R.; Jung, Y. H. *Carbohydr. Res.* **2007**, *342*, 1502; (g) Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2007**, *63*, 2622; (h) Kim, I. S.; Ji, Y. J.; Jung, Y. H. *Tetrahedron Lett.* **2006**, *47*, 7289; (i) Kim, I. S.; Kim, J. D.; Ryu, C. B.; Zee, O. P.; Jung, Y. H. *Tetrahedron* **2006**, *62*, 9349; (j) Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025.
7. Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 903.
8. (a) Welch, W. M.; Kraska, A. R.; Sarges, R.; Koe, B. K. *J. Med. Chem.* **1984**, *27*, 1508; (b) Williams, M.; Quallich, G. *Chem. Ind. (London)* **1990**, *10*, 315; (c) Johnson, B. M.; Chang, P.-T. L. *Anal. Profiles Drug Subst.* **1996**, *24*, 443.
9. (a) Daluge, S.; Good, S.; Faletto, M.; Miller, W.; Wayne, H.; St. Clair, M.; Boone, L.; Tisdale, M.; Parry, N.; Reardon, J.; Dornsife, R.; Averett, D.; Krenitsky, T. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082; (b) Faletto, M.; Miller, W.; Garvey, E.; St. Clair, M.; Daluge, S.; Good, S. *Antimicrob. Agents Chemother.* **1997**, *41*, 1099; (c) Foster, R.; Faulds, D. *Drugs* **1998**, 729; (d) Mahony, W. B.; Domin, B. A.; Daluge, S. M.; Zimmerman, T. P. *Biochem. Pharmacol.* **2004**, *68*, 1797.
10. (a) Schmidt, D. D.; Frommer, W.; Müller, L.; Junge, B.; Wingender, W.; Truscheit, E. *Naturwissenschaften* **1977**, *64*, 535; (b) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem.* **1981**, *93*, 744.
11. General procedure for the reaction of cyclic allylic ether with chlorosulfonyl isocyanate (CSI): To a mixture of cyclic allylic ether (0.53 mmol) in anhydrous CH_2Cl_2 (2 mL, 0.27 M) was added Na_2CO_3 (1.59 mmol, 300 mol %) at 0 °C under N_2. After being stirred for 20 min, CSI (0.80 mmol, 150 mol %) was slowly added at 0 °C under N_2. The reaction mixture was stirred at indicated temperature for reaction time (see Tables 1–4), quenched with H_2O (10 mL) when the reaction was completed (TLC monitoring), and then extracted with EtOAc (25 mL × 2). The organic layer was added to saturated aqueous solution of Na_2SO_3 (10 mL), and the reaction mixture was stirred for 5 h at room temperature. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexanes/EtOAc) to afford product.
12. Selected characterization (**2a**): R_f = 0.14 (*n*-hexanes/EtOAc = 10/1); mp 66.2 °C; IR (KBr) ν 3313, 3034, 2936, 1685, 1531, 1306, 1241, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49–1.68 (m, 3H), 1.88–2.02 (m, 3H), 4.21–4.23 (m, 1H), 4.70–4.72 (m, 1H), 5.10 (s, 2H), 5.59–5.64 (m, 1H), 5.80–5.86 (m, 1H), 7.28–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.51, 24.67, 29.64, 46.27, 66.49, 127.64, 127.99, 128.05, 128.43, 130.74, 136.54, 155.57; HRMS (EI) Calcd for $C_{14}H_{17}NO_2$ $[M]^+$ 231.1259, found 231.1259.